was a mixture (ca. 3:1) of carboxylate epimers. Quantitative cleavage of the benzyl ester was effected by catalytic hydrogenation (10% Pd-C, EtOAc, 1 atm, 25 °C) to give the desired acid **2** (λ_{max}^{Nujol} 5.56, 5.76, and 5.97 μ) as a mixture of carboxylate epimers which were unstable in aqueous solution ($t_{1/2}$ = 2 h; 37 °C; pH 7.0). Despite its instability acid **2** did exhibit antibacterial activity against selected gram-positive and gram-negative organisms. Growth inhibition of *Bacillus subtilis*, *Staphylococcus aureus*, and *Shigella paradysenteriae* was observed at concentrations of 10, 100, and 400 μg/mL, respectively.

Acknowledgment. We are grateful to Mr. Donald H. Pitkin for the in vitro microbiological data presented in this paper.

References and Notes

(1) See for instance (a) S. Wolfe, J.-B. Ducep, K.-C. Tin, and S.-L. Lee, *Can. J. Chem.*, **52**, 3996 (1974), and (b) R. B. Woodward, U.S. Patent 3 835 130 (1974).

(2) For example see (a) L. D. Cama and B. G. Christensen, *J. Am. Chem. Soc.*, **96**, 7582 (1974), and (b) R. N. Guthikonda, L. D. Cama, and B. G. Christensen, *ibid.*, **96**, 7584 (1974).

(3) Elaboration of a monocyclic β-lactam into a bicyclic β-lactam structure has proved to be a useful concept as exemplified by ref 1 and 2 above.

(4) The accompanying communication describes the synthesis of another novel fused-ring β-lactam system from a similar monocyclic β-lactam; D. B. Bryan, R. F. Hall, K. G. Holden, W. F. Huffman, and J. G. Gleason, *J. Am. Chem. Soc.*, following paper in this issue. See also J. Finkelstein, K. G. Holden, R. Sneed, and C. D. Perchonock, submitted for publication.

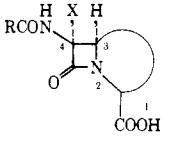
(5) A. K. Bose, J. C. Kapur, S. D. Sharma, and M. S. Manhas, *Tetrahedron Lett.*, 2319 (1973).

(6) Satisfactory spectral data and combustion analysis were obtained for all compounds.

(7) The nitrogen atom can also be protected at this point as a carbamate using such groups as carbobenzyloxy and *tert*-butyloxy.

(8) Simple amides have been oxidatively dealkylated (H. L. Needles and R. E. Whitfield, *J. Org. Chem.*, **29**, 3632 (1964)); however, the use of the dimethoxybenzyl group in this way and its application to β-lactams is new.

(9) These features are illustrated diagramatically in formula i and include: (1)



i

a strained β-lactam resulting from ring fusion, (2) an acylamino function at C-4, (3) cis stereochemistry at C-3,4 (X = H or OCH_3), and (4) a carboxylic acid or its equivalent at C-1.

(10) M. S. Brown and H. Rapoport, *J. Org. Chem.*, **28**, 3261 (1963), and P. L. Hall and R. B. Perfetti, *J. Org. Chem.*, **39**, 111 (1974).

William F. Huffman,* Kenneth G. Holden
Thomas F. Buckley, III, John G. Gleason, L. Wu
Research and Development Division
Smith Kline & French Laboratories
Philadelphia, Pennsylvania 19101

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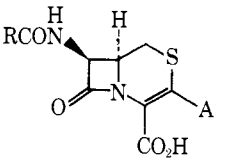
Nuclear Analogues of β-Lactam Antibiotics. 2. The Total Synthesis of 8-Oxo-4-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acids[1]

Sir:

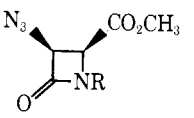
The microorganisms which produce penicillins and Cephalosporin C are capable of producing a limited number of structural modifications; molecules in which the basic heterocyclic ring system is altered are primarily accessible only by total synthesis. We have developed a synthetic approach to such nuclear analogues which allows the stereospecific total synthesis of a number of widely divergent structural types from a single monocyclic β-lactam precursor.[1a,2] In this communication, we report the total synthesis of the *cis*-8-oxo-4-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (isocephalosporin[1b]) nucleus (**1**)[3] which illustrates the versatility of our approach.

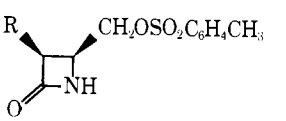


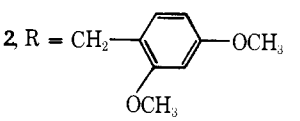
1

The monocyclic *cis*-azetidinone[1a] **2** incorporates both the desired cis stereochemistry as well as the necessary functionalization for subsequent transformation into **1**. The β-lactam nitrogen was deblocked by oxidative cleavage ($K_2S_2O_8$, pH 5-6.5) to afford **3** in high yield.[1a] Selective reduction[4] of the methyl ester with sodium borohydride and tosylation of the resulting alcohol gave *cis*-2-(3-azido-4-oxoazetidenyl)methyl tosylate (**4**). Reduction of the azide (zinc-acetic acid) and coupling of the resulting amine **5** with thienylacetic acid afforded amide **6**: IR (Nujol) ν_{max} 1755 (β-lactam), 1665 cm^{-1} (amide); NMR ($CDCl_3$) δ 8.75 (d, J = 7 Hz, NH), 8.4 (s, β-lactam NH), 6.8-8.0 (m, C_6H_5 + thienyl), 5.1 (dd, J = 4 Hz, 7 Hz, C-3H), 3.8 (m, CH_2-O + C-2H), 3.6 (s, CH_2CO), 2.4 (s, CH_3). Transformation of **6** to the corresponding thiol **9** was achieved by conversion to iodide **7** (sodium iodide, acetone), displacement of the iodide with the sodium salt of trityl mercaptan, and cleavage of the resulting thioether **8** (silver nitrate, methanol).[6]

Alkylation of thiol **9** with benzhydryl β-bromopyruvate[7] afforded the intermediate carbinolamide **10** (IR (film) ν_{max} 1770 (β-lactam), 1750 (ester) and 1650 cm^{-1} (amide)) which on dehydration with thionyl chloride-pyridine gave ester **11** in 14% yield:[8] IR (film) ν_{max} 1760 (β-lactam), 1710 (ester), and 1670 cm^{-1} (amide); NMR ($CDCl_3$) δ 7.2 (m,



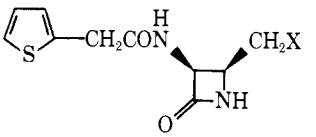




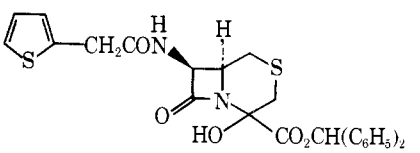
2, R =

4, R = N_3
5, R = H_2N

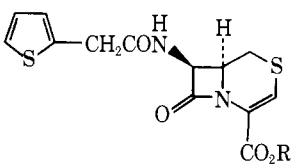
3, R = H



6, X = $OSO_2C_6H_4CH_3$
7, X = I
8, X = $SC(C_6H_5)_3$
9, X = SH

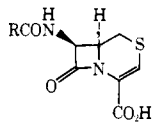
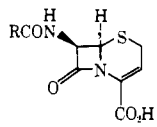
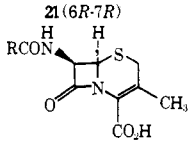


10



11, R = $CHPh_2$
12, R = H

Table I. Minimum Inhibitory Concentrations (MIC) Expressed in μg/mL

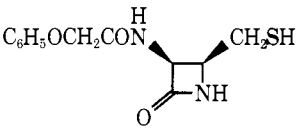
Compound[a]	*Staph. aureus* SK&F 23390	*Strep. faecalis* HH 34358	*E. coli* SK&F 12140	*Kleb. pneumoniae* SK&F 1200	*Salmonella paratyphi* ATCC 12176	*Serratia marcescens* ATCC 13880	*Enterobacter aerogenes* ATCC 13048	*Enterobacter cloacae* HH 31254
 **12** (racemic)[b]	12.5	>200	12.5	6.3	3.1	200	25	25
 **21** (6*R*-7*R*)	1.6	100	25	3.1	3.1	>200	>200	>200
 **22** (6*R*-7*R*)	6.3	>200	100	50	50	>200	>200	>200

[a] R = 2-thienylmethyl for all three compounds. [b] One isomer of **12** would be expected to have twice the activity of the racemic mixture.

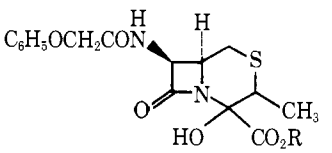
C_6H_5 + thienyl + NH + CH=C), 6.65 (s, $CHPh_2$), 5.4 (dd, $J_{6,7}$ = 5 Hz, $J_{7\text{-NH}}$ = 6 Hz, C-7H), 3.7 (m, C-6H), 3.65 (s, CH_2CO), 2.65 (m, CH_2S); UV λ_{MeOH}^{max} 307 nm. Cleavage of the benzhydryl ester (CF_3CO_2H, 0 °C, 1 h) gave crystalline *dl-cis*-7-(2-thienylacetamido)-8-oxo-4-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (**12**): mp 206–210°; NMR (acetone-d_6) δ 7.85 (d, J = 8 Hz, NH), 7.25 (q, thienyl C-4H), 6.95 (m, thienyl + SCH=C), 5.55 (dd, $J_{6,7}$ = 5 Hz, C-7H), 3.95 (m, C-6H), 3.85 (s, CH_2CO), 3.1 (m, CH_2S).

A functionalized C-3 methyl group, as is present in naturally occurring cephalosporins, generally leads to compounds possessing enhanced gram negative antibacterial activity.[9] Therefore, the synthesis of corresponding derivatives in the synthetic isocephalosporin series was undertaken. Using a route analogous to that described above, thiol **13** was prepared from amine **5**. Addition of *tert*-butyl 3-bromo-2-oxobutyrate[10] gave a mixture of two diastereomeric carbinolamides **14**. Acylation of the mixture ($(CF_3CO)_2O$, pyridine) caused dehydration of one of the diastereomers to afford **15** in 24% yield: IR (film) 1780 (β-lactam), 1705 (ester) and 1665 cm^{-1} (amide); NMR ($CDCl_3$) δ 7.0 (m, C_6H_5 + NH), 5.4 (dd $J_{6,7}$ = 5 Hz, $J_{7\text{-NH}}$ = 7 Hz, C-7H), 4.52 (s, OCH_2CO), 4.0 (m, C-6H), 2.8 (m, CH_2S), 2.2 (s, CH_3), 1.5 (s, $C(CH_3)_3$). The unreactive carbinolamide diastereomer, which was recovered unchanged, presumably was the 3β-methyl isomer. Acids **16** and **17** were obtained by ester cleavage (TFA, anisole, 0 °C, 1 h). Functionalization of the C-3 methyl was achieved by free radical bromination[11] (NBS, AIBN, or $(C_6H_5CO_2)_2$; CCl_4, 70 °C, 2 h) of the ester **15**. The isolable, but unstable, 3-bromomethyl derivative **18** (NMR ($CDCl_3$) δ 4.4 (ABq, J = 10 Hz, CH_2Br) reacted with potassium acetate (acetonitrile, 18-crown-6, room temperature, 1 h)[12] to give the 3-acetoxymethyl ester **19**: IR (film) ν_{max} 1770 (β-lactam), 1745 (acetate), 1695 (ester), and 1670 cm^{-1} (amide); NMR ($CDCl_3$) δ 7.0 (m, C_6H_5 + NH), 5.4 (dd, $J_{6,7}$ = 5 Hz, $J_{7\text{-NH}}$ = 6 Hz, C-7H), 4.95 (ABq, J = 14 Hz, CH_2OAc), 4.5 (s, OCH_2CO), 4.0 (m, C-6H), 2.85 (m, CH_2S), 2.05 (s, CH_3CO), 1.5 (s, $C(CH_3)_3$). Removal of the *tert*-butyl ester (CF_3CO_2H, CH_2Cl_2, room temperature, 1 h) gave *dl-cis*-7-phenoxyacetamido-3-acetoxymethyl-8-oxo-4-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, **20**: IR (CH_2Cl_2) ν_{max} 1765 cm^{-1} (β-lactam).

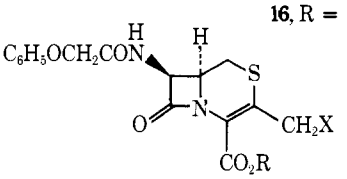
All of the isocephalosporin acids, with the exception of **16**, exhibited good antibacterial activity against *B. subtilis* and penicillin resistant *Staphylococcus aureus*. Table I compares



13



14, R = *t*-Bu
16, R = H



15, R = *t*-Bu; X = H
17, R = H; X = H
18, R = *t*-Bu; X = Br
19, R = *t*-Bu; X = OAc
20, R = H; X = OAc

the antibacterial spectrum of racemic **12** to the analogous, optically active cephalosporins **21**[13] and **22** derived from natural sources. Thus, unlike the 1-oxacephalothin and 1-carbocephalothin nuclei whose antimicrobial activity directly parallels the natural nucleus,[14] the totally synthetic **12** appears to be generally more active than the natural nucleus against the gram negative bacteria while showing somewhat diminished activity against *Staph. aureus* and *Strep. faecalis*.

Acknowledgment. We are grateful to Drs. J. Kerwin and H. Rapoport for helpful discussions during the course of this work. We thank F. Owings of our Organic Chemistry department for large scale synthesis of **2**, S. Fagan and K. Erhard for preparation of important intermediates, and J. Guarini for the in vitro results reported in this paper.

References and Notes

(1) (a) For part 1, see W. F. Huffman, K. G. Holden, T. F. Buckley III, J. G. Gleason, and L. Wu, *J. Am. Chem. Soc.*, preceding paper in this issue. (b) For convenience, we have used the trivial name of isocephalosporin for the 7-acylamino-8-oxo-4-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate nucleus.
(2) J. Finkelstein, K. G. Holden, R. Sneed, and C. D. Perchonock, submitted for publication.
(3) A 7α-methyl isocephalosporin has been described; however, the compound was biologically inactive. Attempts to prepare a cis isocephalosporin were unsuccessful; see D. M. Brunwin and G. Lowe *J. Chem. Soc., Perkin Trans. 1*, 1321 (1973).

(4) M. S. Brown and H. Rapoport, *J. Org. Chem.*, **28**, 3261 (1963); D. L. Hall and R. B. Perfetti, *ibid.*, **39**, 111 (1974).
(5) Satisfactory elemental analyses were obtained for compounds **4**, **6**, **7**, **9**, **12**, and **15**. All other compounds were characterized by spectroscopic methods.
(6) L. Zervas and I. Photaki, *J. Am. Chem. Soc.*, **84**, 3887 (1962).
(7) Prepared by esterification of bromopyruvic acid with diphenyldiazomethane in benzene at room temperature.
(8) Difficulties in similar dehydrations have been reported. See, for example, German patent 2 337 447.
(9) M. Gorman and C. W. Ryan in "Cephalosporins and Penicillins; Chemistry and Biology", E. H. Flynn, Ed., Academic Press, New York, N.Y., 1972, Chapter 12.
(10) Prepared by esterification of 3-bromo-2-oxobutyric acid with *N,N'*-diisopropyl-*O*-*tert*-butylpseudourea in methylene chloride at room temperature for 2 days.
(11) Functionalization of 3-methyl-3-cephem esters by allylic bromination falls although 2-cephem esters may be functionalized in this way: J. A. Webber, G. W. Huffman, R. E. Koehler, C. F. Murphy, C. W. Ryan, E. M. Van Heyningen, and R. T. Vasileff, *J. Med. Chem.*, **14**, 113 (1971); see also ref 9, Chapter 4.
(12) C. L. Liotta, H. P. Harris, M. McDermott, T. Gonzalez, and K. Smith, *Tetrahedron Lett.*, 2417 (1974).
(13) Unpublished data, J. Hoover and D. Jakas.
(14) L. D. Cama and B. G. Christensen, *J. Am. Chem. Soc.*, **96**, 7582 (1974); R. N. Guthikonda, L. D. Cama, and B. G. Christensen, *J. Am. Chem. Soc.*, **96**, 7584 (1974).

D. Boles Bryan, Ralph F. Hall, Kenneth G. Holden
William F. Huffman, John G. Gleason*
Research & Development Division
Smith Kline & French Laboratories
Philadelphia, Pennsylvania 19101
Received October 26, 1976

Decarboxylative 1-Aza-1'-oxa [3,3]Sigmatropic Rearrangements of Enolizable or Enolized *N*-Aryl-*N,O*-diacylhydroxylamines to *o*-(*N*-Acylamino)aryl Ketones, Esters, and Amides: a New Synthetic Method for Ortho Alkylation

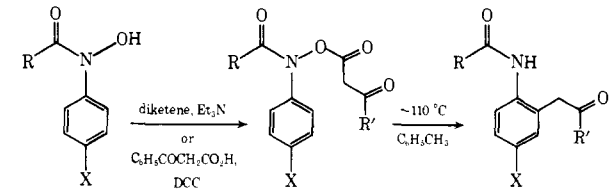
Sir:

The introduction of allyl substituents into the ortho position of phenols by the Claisen rearrangement of allyl aryl ethers is a long-known and effective synthetic process.[1] Although the scope of the more recently discovered amino-Claisen rearrangement for the synthesis of ortho allyl anilines is at present less well defined,[2] the high temperatures or acid catalysts usually employed for this reaction would appear to impose certain limitations on its utility, and indeed a number of side reactions have already been encountered.[3] The ortho alkylation of anilines may also be accomplished through [2,3]sigmatropic rearrangements of N-aryl azasulfonium ylides albeit with a subsequent reduction to remove the sulfur function from the side chain.[4] We wish to report a new regiospecific synthesis of anilides having carbonyl-functionalized alkyl groups in the ortho position by means of 1-aza-1'-oxa [3,3]sigmatropic rearrangements[5] of enolizable or enolized *N*-aryl-*N,O*-diacylhydroxylamines.

Although a number of reactions which appear to involve rearrangements of this type has been reported in the literature,[6,7] apart from the acid-catalyzed isomerization of O-aryl ketoximes to *o*-hydroxyphenylketimines or benzofurans,[6c] the synthetic applications of this 1'-aza analogue of the Claisen rearrangement have been restricted. One factor which has no doubt impeded the exploitation of this inherently exothermic transformation[8] is the instability of the requisite *N,O*-divinyl- and *N*-aryl-*O*-vinylhydroxylamines. Accordingly we choose to model our initial approach after the Carroll reaction,[9] a variant of the Claisen rearrangement in which the vinyl ether grouping is generated simply by enolization of an allyl acetoacetate.

N-Aryl-*N*-hydroxyamides (**1**), readily available by partial reduction of nitroarenes to *N*-arylhydroxylamines[10,11] and selective N-acylation,[11,12] are transformed into *O*-acetoacetyl derivatives (**2**) by reaction with diketene in the presence of a catalytic amount of triethylamine (1.1 equiv of diketene, 1:1 chloroform–ether, 0 °C, overnight). The two phenyl substituted intermediates (**2c** and **2e**) were obtained in a complementary manner by the dicyclohexylcarbodimide(DCC)-induced condensation of benzoylacetic acid with the appropriate *N*-hydroxy amides. Since these compounds proved, with two exceptions, to be liquids and rather unstable, they were for the most part purified only by extraction (5–10% sodium bicarbonate) to remove any unreacted *N*-hydroxyamide and characterized chiefly by infrared and NMR spectral data.[13]

Scheme I



	1			2	3
	X	R	R'	Yield (%)	Yield (%)
a	H	CH_3	CH_3	71	55
b	H	C_6H_5	CH_3	77	46
c	H	CH_3	C_6H_5	—[a]	51[b]
d	CH_3	CH_3	CH_3	81	82
e	CH_3	CH_3	C_6H_5	—[a]	50[b]
f	CH_3	C_6H_5	CH_3	88	61
g	Cl	CH_3	CH_3	85	44
h	CO_2CH_3	CH_3	CH_3	70	40

[a] Yield not determined at this stage. [b] Overall yield from 1.

When heated in toluene at reflux temperature (~110 °C for 30–90 min, the β-keto esters undergo decarboxylation and give rise to *o*-(*N*-acylamino)aryl ketones (**3**) as major products in 40–82% yield after purification by chromatography on silica gel.[13b,14] Two of the products were identified as the known 2'-acetonylacetanilide (**3**, X = H; R = R' = CH_3; mp 134–136 °C)[15a] and 2'-acetonylbenzanilide (**3**, X = H; R = C_6H_5; R' = CH_3; mp 115–117 °C)[15b] by the correspondence of melting points and spectral data. The structural assignments for the others are based upon the similarity of the spectra and analogy.

According to the analogy with the Carroll reaction,[9] one plausible mechanism for this reaction consists of a [3,3]sigmatropic rearrangement of the ketene hemiacetal tautomer **4**, prototropic rearomatization, and decarboxylation of the resulting β-keto acid intermediate. Although the apparent absence of appreciable amounts of the para isomer of **3**[16] would seem inconsistent with a dissociative mechanism involving free radicals or ions, the possibility of radical or ion pair pathways cannot be discounted. It is pertinent to note that these reactions occur at much lower temperature (~110 °C as opposed to ≥ 150 °C) than is required to isomerize *N*-aryl-*N,O*-diacylhydroxylamines to *o*-acyloxyanilides[17] and that there are indications that the ortho alkylation step precedes decarboxylation (see below).

Hydrolysis of four of the *o*-(*N*-acylmino)aryl ketones (**3a**, **3c**, **3d**, and **3g**) with 10% hydrochloric acid in 95% ethanol for 15 min at reflux afforded the corresponding substituted indoles in 79–91% yield, a reaction which provides both additional support for the structures proposed and a practical application for the 1'-aza Claisen rearrangement. In this connection it is noteworthy that the uncyclized ketones (**3**) produced in this ortho alkylation reaction (**2** → **3**) may be isolated and, in principle, utilized for other purposes, in contrast to the spontaneous cyclization which occurs in the Fischer[18] and Gassman[4b,d] indole syntheses. The only alternative synthesis of *o*-(*N*-acylamino)aryl ketones (**3**) of which we are aware